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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/232,290	01/15/1999	ANDREAS PLUCKTHUN	MORPHO/7	1987

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EXAMINER

HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 08/01/2003

38

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/232,290

Applicant(s)

PLUCKTHUN ET AL.

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 May 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5,8-27 and 37-41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5,8-27 and 37-41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- ☐ Interview Summary (PTO-413) Paper No(s). _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other:

DETAILED ACTION

1. Claim 7 has been canceled.
Claims 1, 4, 8-12, 37-38 have been amended.
Claims 39-41 have been added.
2. Claims 1-5, 8-27, 37-41 are pending and under examination.
3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.
4. The following Office Action contains NEW GROUNDS of rejection.

Specification

5. The substitute specification filed 8/29/02 has been entered.

Drawings

6. In the response filed 8/29/02 the amendment stated that a corrected Figure 1 was supplied and figures 2a and 2 b have been amended. The examiner does not find the corrected figures of marked up copies of the figures.

Response to Arguments

7. The rejection of claims 1-5, 8-11, 13-17, 26-27, 37-38 and newly added claim 41 under 102(b) as being anticipated by Johnson (WO 92/01787) is maintained.

The response filed 5/19/03 has been carefully considered but is deemed not to be persuasive. The response states that the pending claims are directed to "inter

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domain" interface which is defined at page 4., lines 1-7 as the interface that exists between VH/CH1 or VL/CL (see page 7-8 of response). In response to this argument, the claims are not restricted to this interface and as such the VH/VL interface is encompassed by the claims. The response further states that Johnson does not teach a first variable domain capable of interacting with a second variable domain and Johnson only teaches modification of the VH domain. In response to this argument, Johnson teaches alterations in the VH or VL interface and the fragments are capable of binding antigen (see page 10, 13, of Johnson). The response further states that Johnson's definition of an antibody is not a Fab or scFv and Johnson does not mention once a Fab or scFv outside the passage on page 13 (see page 9-10 of response). In response to this argument, one reading Johnson would know that in the description of the interface on page 13, any of those fragments would have such an interface and could be used. The response further states that Johnson is limited to unpaired single domains (see page 11 of response). In response to this argument, Johnson clearly contemplates the association between the VH and VL as shown in page 10, lines 15-25. The response further states that the declaration of Dr. Pluckthun describes Johnson's modification and that such modifications would not result in a two variable domain antibody (see pages 12-13 of response. The declaration of Dr. Pluckthun has been carefully considered but is deemed not to be persuasive. The declaration and the response directed to the declaration is not persuasive because as taught by Johnson that if the molecule is an antibody or binding domain the hydrophobic amino acids can be chosen for alteration to a hydrophilic amino acid by examining the molecule for

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hydrophobic amino acids which are buried in the interface between the heavy and light chains (see page 10) and as such Johnson clearly teaches alteration in the interface region of an antibody.

8. The rejection of claims 1-5, 8-27, 37-38 under 103(a) as being unpatentable over Johnson (WO 92/01787) in view of Jenkins et al (PNAS 92:6057-61, 1995) and Knappik et al (Biotechniques 17:747-61, 1994) and Dubel et al (J Of Immunological methods 178:201-209, 1995) and Kostelny et al (J Of Immunol 148:1547-1553, 1992) is maintained.

The response filed 5/19/03 has been carefully considered but is deemed not to be persuasive. The response states Johnson does not teach or suggest functional antibody formats with a variable domain that is capable of interacting with a second variable domain to form a functional molecule (see page 13 of response). In response to this argument, the argument has been addressed in the above rejection.

The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-5, 13-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 and those dependent on claim 1 are indefinite for reciting "functional fragment" because the exact meaning of the phrase is not clear. Does the phrase mean an antigen binding fragment, or a fragment such as a variable domain or a fragment with some other function such as ADCC or some other function?

b. Claims 1 and those claims dependent on claim 1 and claim 39-40 are indefinite for reciting "capable of interacting" because the exact meaning of the phrase is not clear. Does the first variable domain interact with a second variable domain or not?

c. Claims 2 and 4 recites the limitation "said region" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

d. Claim 17 recites the limitation "said surface protein" in claim 6. There is insufficient antecedent basis for this limitation in the claim.

e. Claims 39-40 are indefinite for reciting "a modified former interface" because the exact meaning of the phrase is not clear. Does the phrase mean the modified region is no longer an interface or modification results in it no longer being an interface or some other meaning?

f. Claims 39-40 recites the limitation "said modification". There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

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12. Claim 27 is rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claim 27, as written, does not sufficiently distinguish over cells as they exist naturally because claim does not particularly point out any non-naturally occurring differences between the claimed cell and the structure of naturally occurring cells.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claim to recite "an isolated" or "purified" host cell or similar language would obviate this rejection.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical

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Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000.

Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. Claims 1-2, 4-5, 8-9, 12-13, 26-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Stevens et al (US Patent 6,485,943, with priority to 1/95).

The claims are summarized as a DNA molecule encoding an antibody wherein the antibody has a modification in the inter-domain interface which increases the hydrophilicity compared to the parent antibody wherein the modification is a substitution of a more hydrophilic amino acid and the antibody fragment is a Fab or Fv and the interface comprises residues recited in the claims and the DNA encodes an additional moiety and a vector comprising such and a host cell.

Stevens et al teach alterations in the domain interface of an antibody Fab or Fv or antibody wherein alteration is a substitution of a charged residue which would inherently be more hydrophilic and the fragment can be an entire antibody which reads on claim 13 and vectors and host cells comprising such (see column 4, 6).

Claim Rejections - 35 USC § 103

15. Claims 1-5, 8-27, 37-38 and 41 are rejected under 103(a) as being unpatentable over Stevens et al (US Patent 6,485,943, priority to 1/95) in view of Jenkins et al (PNAS 92:6057-61, 1995) and Knappik et al (Biotechniques 17:747-61, 1994) and Dubel et al

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(J Of Immunological methods 178:201-209, 1995) and Kostelny et al (J Of Immunol 148:1547-1553, 1992).

Stevens has been described supra. Stevens does not teach a DNA further comprising an additional moiety capable of binding a metal ion, a peptide or labeling Tag moiety or five histidines or C-myc or FLAG or leucine zippers. These deficiencies are made up for in the teachings of Jenkins et al, Knappik et al, Dubel et al and Kostelny et al.

Jensen et al teach DNA methods of producing mutants by replacing hydrophobic residues to increase solubility and recombinant methods of adding histidine tag for purification of the protein.

Knappik et al teach the use of the FLAG peptide for detection and purification of antibodies.

Dubel et al teach scFv containing cysteine to produce multimeric molecules.

Kostelny et al teach DNA comprising leucine zippers to Fab fragments for production of homodimers.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced DNA encoding a modified interface as taught by Stevens et al and add a peptide moiety as taught by Jenkins et al, Knappik et al, Dubel et al and Kostelny et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced DNA encoding a modified interface as taught by Stevens et al and add a peptide moiety as taught by Jenkins et al,

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Knappik et al, Dubel et al and Kostelny et al because it was obvious to add a moiety to the DNA which encodes a peptide for purification or detection as demonstrated by Knappik et al with the FLAG peptide and Jensen with the histidine tag. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced DNA encoding a modified interface as taught by Stevens et al and add a peptide moiety as taught by Jenkins et al, Knappik et al, Dubel et al and Kostelny et al because Dubel et al teach multivalent fragments which bind tighter than monovalent and Kostelny et al teach homodimers for immunotherapy which are advantageous over monovalent.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of

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this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D.
PRIMARY EXAMINER



LARRY R. HELMS, PH.D.
PRIMARY EXAMINER